	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	421	aberrant adj splicing	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/26 16:00			0
2	BRS	L2	179	1 same cell	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/26 16:02			0
3	BRS	L3	6571	cystic adj fibrosis	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/26 16:01			0
4	BRS	L4	1835	(alternative adj splicing adj factor) or asf	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/26 16:11			0
5	BRS	L6	128	2 same disease	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/26 16:02			0
6	BRS	L7	36	SR adj protein	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/26 16:03			0
7	BRS	L8	20	(heterogeneous adj nuclear adj ribonucleoprotein adj a1) or hbrnpa1	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/26 16:05			0
8	BRS	L9	14	E4-ORF3 or E4-ORF6	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/26 16:05			0
9	BRS	L5	2	3 same 4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/26 16:06			0
10	BRS	L10	3	(6 or 3) same (4 or 7 or 8 or 9)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/26 16:10			0
11	BRS	L11	7	alternative adj splicing adj factor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/07/26 16:11			0

> d his

(FILE 'HOME' ENTERED AT 16:14:57 ON 26 JUL 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
16:15:24 ON 26 JUL 2002
L1 197 S ALTERNATIVE SPLICING FACTOR
L2 2978 S (SR PROTEIN) OR (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1)
L3 87512 S CYSTIC FIBROSIS
L4 1655 S ABERRANT SPLICING
L5 598 S L4 (P) CELL
L6 1479108 S GENE (P) EXPRESSION
L7 203 S L5 (P) L6
L8 203 S L7 (P) L4
L9 6 S L3 (P) L7
L10 32 S L7 (P) DISEASE
L11 0 S (L9 OR L10) (P) (L1 OR L2)
L12 20 S L3 (P) (L1 OR L2)
L13 5 DUPLICATE REMOVE L12 (15 DUPLICATES REMOVED)

=> log y

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FILE 'HOME' ENTERED AT 16:26:33 ON 26 JUL 2002

=> file medline caplus biosis embase scisearch agricola
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'MEDLINE' ENTERED AT 16:27:04 ON 26 JUL 2002

FILE 'CAPLUS' ENTERED AT 16:27:04 ON 26 JUL 2002
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FILE 'AGRICOLA' ENTERED AT 16:27:04 ON 26 JUL 2002

=> s alternative splicing factor
L1          197 ALTERNATIVE SPLICING FACTOR

=> s (sr protein) or (heterogeneous nuclear ribonucleoprotein A1) or E4-ORF3 or E4-ORF6
L2         2978 (SR PROTEIN) OR (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1) OR
                E4-ORF3 OR E4-ORF6

=> s cystic fibrosis
L3        87512 CYSTIC FIBROSIS

=> s (l1 or l2) (p) l3
L4           20 (L1 OR L2) (P) L3

=> duplicate remove l4
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L4
L5             5 DUPLICATE REMOVE L4 (15 DUPLICATES REMOVED)

=> d l5 1-5 ibib abs

L5   ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:123508  CAPLUS
DOCUMENT NUMBER:          136:162403
TITLE:                    Control of aberrant gene expression by alternative
                          splicing factor
INVENTOR(S):              Kerem, Batsheva
PATENT ASSIGNEE(S):       Yissum Research Development Company of the Hebrew
                          University of Jerusalem, Israel
SOURCE:                   U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of U.S.
                          Ser. No. 421,891, abandoned.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     US 2002018768      A1   20020214       US 2001-871809   20010604
PRIORITY APPLN. INFO.:                    US 1999-421891   B2 19991021
AB   The invention concerns a method for treating various genetic diseases
     caused by aberrant splicing by utilizing factors which can modulate
     alternative splicing.  The method of the present invention is esp.
```

suitable for the treatment of cystic fibrosis.

L5 ANSWER 2 OF 5 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001229125 MEDLINE
DOCUMENT NUMBER: 21181834 PubMed ID: 11285240
TITLE: Nuclear factor TDP-43 and SR proteins promote in vitro and in vivo CFTR exon 9 skipping.
AUTHOR: Buratti E; Dork T; Zuccato E; Pagani F; Romano M; Baralle F E
CORPORATE SOURCE: International Centre for Genetic Engineering and Biotechnology (ICGEB), Padriciano 99, 34012 Trieste, Italy.
SOURCE: EMBO JOURNAL, (2001 Apr 2) 20 (7) 1774-84.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered Medline: 20010607

AB Alternative splicing of human ***cystic*** ***fibrosis*** transmembrane conductance regulator (CFTR) exon 9 is regulated by a combination of cis-acting elements distributed through the exon and both flanking introns (IVS8 and IVS9). Several studies have identified in the IVS8 intron 3' splice site a regulatory element that is composed of a polymorphic (TG)m(T)n repeated sequence. At present, no cellular factors have been identified that recognize this element. We have identified TDP-43, a nuclear protein not previously described to bind RNA, as the factor binding specifically to the (TG)m sequence. Transient TDP-43 overexpression in Hep3B cells results in an increase in exon 9 skipping. This effect is more pronounced with concomitant overexpression of ***SR*** ***proteins*** . Antisense inhibition of endogenous TDP-43 expression results in increased inclusion of exon 9, providing a new therapeutic target to correct aberrant splicing of exon 9 in CF patients. The clinical and biological relevance of this finding in vivo is demonstrated by our characterization of a CF patient carrying a TG10T9(DeltaF508)/TG13T3(wt) genotype leading to a disease-causing high proportion of exon 9 skipping.

L5 ANSWER 3 OF 5 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000396647 MEDLINE
DOCUMENT NUMBER: 20347209 PubMed ID: 10766763
TITLE: Splicing factors induce cystic fibrosis transmembrane regulator exon 9 skipping through a nonevolutionary conserved intronic element.
AUTHOR: Pagani F; Buratti E; Stuani C; Romano M; Zuccato E; Niksic M; Giglio L; Faraguna D; Baralle F E
CORPORATE SOURCE: International Centre for Genetic Engineering and Biotechnology, Padriciano 99 and IRCCS, Burlo Garofolo, via dell'Istria 65/1, Trieste, TS 34012 Italy.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Jul 14) 275 (28) 21041-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20000824
Entered Medline: 20000816

AB In monosymptomatic forms of ***cystic*** ***fibrosis*** such as congenital bilateral absence of vas deferens, variations in the TG(m) and T(n) polymorphic repeats at the 3' end of intron 8 of the ***cystic*** ***fibrosis*** transmembrane regulator (CFTR) gene are associated with the alternative splicing of exon 9, which results in a nonfunctional CFTR protein. Using a minigene model system, we have previously shown a direct relationship between the TG(m)T(n) polymorphism and exon 9 splicing. We have now evaluated the role of splicing factors in the regulation of the alternative splicing of this exon. Serine-arginine-rich proteins and the ***heterogeneous*** ***nuclear*** ***ribonucleoprotein***

A1 induced exon skipping in the human gene but not in its mouse counterpart. The effect of these proteins on exon 9 exclusion was strictly dependent on the composition of the TG(m) and T(n) polymorphic repeats. The comparative and functional analysis of the human and mouse CFTR genes showed that a region of about 150 nucleotides, present only in the human intron 9, mediates the exon 9 splicing inhibition in association with exonic regulatory elements. This region, defined as the CFTR exon 9 intronic splicing silencer, is a target for serine-arginine-rich protein interactions. Thus, the nonevolutionary conserved CFTR exon 9 alternative splicing is modulated by the TG(m) and T(n) polymorphism at the 3' splice region, enhancer and silencer exonic elements, and the intronic splicing silencer in the proximal 5' intronic region. Tissue levels and individual variability of splicing factors would determine the penetrance of the TG(m)T(n) locus in monosymptomatic forms of ***cystic*** ***fibrosis*** .

DUPLICATE 3

L5 ANSWER 4 OF 5 MEDLINE

ACCESSION NUMBER: 2001014733 MEDLINE
DOCUMENT NUMBER: 20377488 PubMed ID: 10915765
TITLE: Cellular and viral splicing factors can modify the splicing pattern of CFTR transcripts carrying splicing mutations.
AUTHOR: Nissim-Rafinia M; Chiba-Falek O; Sharon G; Boss A; Kerem B
CORPORATE SOURCE: Department of Genetics, Life Sciences Institute, The Hebrew University, Jerusalem 91904, Israel.
SOURCE: HUMAN MOLECULAR GENETICS, (2000 Jul 22) 9 (12) 1771-8. Journal code: 9208958. ISSN: 0964-6906.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001027

AB Variable levels of aberrantly spliced ***cystic*** ***fibrosis*** transmembrane conductance regulator (CFTR) transcripts were suggested to correlate with variable ***cystic*** ***fibrosis*** (CF) severity. We studied the effect of the cellular splicing factors, hnRNP A1 and ASF/SF2, and their adenoviral analogues, ***E4*** - ***ORF6*** and ***E4*** - ***ORF3*** , that promote exon skipping and/or exon inclusion, on the splicing pattern of the CFTR mutation 3849+10kb C-->T and the 5T allele. These mutations can lead to cryptic exon inclusion and exon skipping, respectively. Overexpression of the cellular factors promoted exon skipping of pre-mRNA transcribed from minigenes carrying the mutation (p5T or p3849M). This led to a substantial decrease in the level of correctly spliced mRNA transcribed from p5T and generated correctly spliced mRNA transcribed from p3849M that was not found without overexpression of the factors. The viral factor, ***E4*** - ***ORF3*** , promoted exon inclusion and led to a substantial increase of the correctly spliced mRNA transcribed from the p5T. The factor, ***E4*** - ***ORF6*** , activated exon skipping and generated correctly spliced mRNA transcribed from p3849M. Thus, overexpression of ***alternative*** ***splicing*** ***factors*** can modulate the splicing pattern of CFTR alleles carrying splicing mutations. These results are important for understanding the mechanism underlying phenotypic variability in CF and other genetic diseases.

DUPLICATE 4

L5 ANSWER 5 OF 5 MEDLINE

ACCESSION NUMBER: 1999412346 MEDLINE
DOCUMENT NUMBER: 99412346 PubMed ID: 10482581
TITLE: Regulation of adenovirus-mediated transgene expression by the viral E4 gene products: requirement for E4 ORF3.
AUTHOR: Lusky M; Grave L; Dieterle A; Dreyer D; Christ M; Ziller C; Furstenberger P; Kintz J; Hadji D A; Pavirani A; Mehtali M
CORPORATE SOURCE: TRANSGENE S.A., 67085 Strasbourg, France.
SOURCE: JOURNAL OF VIROLOGY, (1999 Oct) 73 (10) 8308-19. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910

ENTRY DATE: Entered STN: 19991026
Last Updated STN: 19991026
Entered Medline: 19991012

AB In a previous study we showed that multiple deletions of the adenoviral regulatory E1/E3/E4 or E1/E3/E2A genes did not influence the in vivo persistence of the viral genome or affect the antiviral host immune response (Lusky et al., J. Virol. 72:2022-2032, 1998). In this study, the influence of the adenoviral E4 region on the strength and persistence of transgene expression was evaluated by using as a model system the human ***cystic*** ***fibrosis*** transmembrane conductance regulator (CFTR) cDNA transcribed from the cytomegalovirus (CMV) promoter. We show that the viral E4 region is indispensable for persistent expression from the CMV promoter in vitro and in vivo, with, however, a tissue-specific modulation of E4 function(s). In the liver, E4 open reading frame 3 (ORF3) was necessary and sufficient to establish and maintain CFTR expression. In addition, the ***E4*** ***ORF3*** -dependent activation of transgene expression was enhanced in the presence of either E4 ORF4 or ***E4*** ***ORF6*** and ORF6/7. In the lung, establishment of transgene expression was independent of the E4 gene products but maintenance of stable transgene expression required ***E4*** ***ORF3*** together with either E4 ORF4 or ***E4*** ***ORF6*** and ORF6/7. Nuclear run-on experiments showed that initiation of transcription from the CMV promoter was severely reduced in the absence of E4 functions but could be partially restored in the presence of either ORF3 and ORF4 or ORFs 1 through 4. These results imply a direct involvement of some of the E4-encoded proteins in the transcriptional regulation of heterologous transgenes. We also report that C57BL/6 mice are immunologically weakly responsive to the human CFTR protein. This observation implies that such mice may constitute attractive hosts for the in vivo evaluation of vectors for ***cystic*** ***fibrosis*** gene therapy.

=> d his

(FILE 'HOME' ENTERED AT 16:26:33 ON 26 JUL 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 16:27:04 ON 26 JUL 2002

L1 197 S ALTERNATIVE SPLICING FACTOR
L2 2978 S (SR PROTEIN) OR (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1)
L3 87512 S CYSTIC FIBROSIS
L4 20 S (L1 OR L2) (P) L3
L5 5 DUPLICATE REMOVE L4 (15 DUPLICATES REMOVED)

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	32.17	32.38
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.62	-0.62

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=> file medline caplus biosis embase scisearch agricola
                                                  SINCE FILE      TOTAL
COST IN U.S. DOLLARS                                 ENTRY     SESSION
                                                      0.21        0.21

FULL ESTIMATED COST

FILE 'MEDLINE' ENTERED AT 16:15:24 ON 26 JUL 2002

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FILE 'AGRICOLA' ENTERED AT 16:15:24 ON 26 JUL 2002

=> s alternative splicing factor
L1          197 ALTERNATIVE SPLICING FACTOR

=> s (sr protein) or (heterogeneous nuclear ribonucleoprotein A1) or E4-ORF3 or E4-ORF6
   4 FILES SEARCHED...
L2         2978 (SR PROTEIN) OR (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1) OR
                E4-ORF3 OR E4-ORF6

=> s cystic fibrosis
L3        87512 CYSTIC FIBROSIS

=> s aberrant splicing
L4         1655 ABERRANT SPLICING

=> s l4 (p) cell
L5          598 L4 (P) CELL

=> s gene (p) expression
L6      1479108 GENE (P) EXPRESSION

=> s L5 (p) l6
L7          203 L5 (P) L6

=> s l7 (p) l4
L8          203 L7 (P) L4

=> s l3 (p) l7
L9            6 L3 (P) L7

=> s l7 (p) disease
L10          32 L7 (P) DISEASE

=> d his

     (FILE 'HOME' ENTERED AT 16:14:57 ON 26 JUL 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     16:15:24 ON 26 JUL 2002
L1           197 S ALTERNATIVE SPLICING FACTOR
L2          2978 S (SR PROTEIN) OR (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1)
L3         87512 S CYSTIC FIBROSIS
L4          1655 S ABERRANT SPLICING
L5           598 S L4 (P) CELL
L6       1479108 S GENE (P) EXPRESSION
L7           203 S L5 (P) L6
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L8          203 S L7 (P) L4
L9            6 S L3 (P) L7
L10          32 S L7 (P) DISEASE

=> s (l9 or l10) (p) (l1 or l2)
L11           0 (L9 OR L10) (P) (L1 OR L2)

=> s l3 (p) (l1 or l2)
L12          20 L3 (P) (L1 OR L2)

=> duplicate remove l12
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L12
L13            5 DUPLICATE REMOVE L12 (15 DUPLICATES REMOVED)

=> d l13 ibib abs

L13  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:123508  CAPLUS
DOCUMENT NUMBER:          136:162403
TITLE:                    Control of aberrant gene expression by alternative
                          splicing factor
INVENTOR(S):              Kerem, Batsheva
PATENT ASSIGNEE(S):       Yissum Research Development Company of the Hebrew
                          University of Jerusalem, Israel
SOURCE:                   U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of U.S.
                          Ser. No. 421,891, abandoned.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
     US 2002018768      A1   20020214       US 2001-871809    20010604
PRIORITY APPLN. INFO.:                   US 1999-421891   B2 19991021
AB   The invention concerns a method for treating various genetic diseases
     caused by aberrant splicing by utilizing factors which can modulate
     alternative splicing.  The method of the present invention is esp.
     suitable for the treatment of cystic fibrosis.


=> d his

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     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     16:15:24 ON 26 JUL 2002
L1           197 S ALTERNATIVE SPLICING FACTOR
L2          2978 S (SR PROTEIN) OR (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1)
L3         87512 S CYSTIC FIBROSIS
L4          1655 S ABERRANT SPLICING
L5           598 S L4 (P) CELL
L6       1479108 S GENE (P) EXPRESSION
L7           203 S L5 (P) L6
L8           203 S L7 (P) L4
L9             6 S L3 (P) L7
L10           32 S L7 (P) DISEASE
L11            0 S (L9 OR L10) (P) (L1 OR L2)
L12           20 S L3 (P) (L1 OR L2)
L13            5 DUPLICATE REMOVE L12 (15 DUPLICATES REMOVED)

=> log y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY     SESSION
FULL ESTIMATED COST                                   48.96       49.17

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY     SESSION
CA SUBSCRIBER PRICE                                   -0.62       -0.62
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